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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/194,053	11/23/1998	MOHAMED CHOKRI	USB96AKIDM	2743

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/194,053	CHOKRI ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,49,50 and 91-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,49,50 and 91-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments, remarks, and 1.132 declaration of Dr. Michael Lotze, filed 2/02/05 are acknowledged.

2. Claims 44, 49, 50, and newly added Claims 91-104 are pending.

3. In view of Applicant's Amendments and Remarks, filed 2/02/05, the previous rejections under the second paragraph of 35 U.S.C. 112 have been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44, 49, 50, and newly added Claims 91-104, stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record as set forth in the paper mailed 7/29/02 and maintained in the papers mailed 5/07/03 and 8/02/04.

As set forth previously, the instant invention is drawn to a previously undescribed type of antigen presenting cell that possesses properties of both macrophages, i.e., phagocytic capacity, and dendritic cells, i.e., superior antigen presentation. Given the unexpected nature of the cell of the instant claims, said cell must be considered highly unpredictable. As such, an enabling specification would require significant guidance and direction, and/or working examples. The specification, however, fails to adequately disclose to one of skill in the art how to make the invention of the instant claims as broadly claimed, or even that the MD-APCs of the instant claims indeed exist as a single, specific, cell type.

The specification discloses that the MD-APCs of the instant claims are produced by a method of culturing monocytes in a medium comprising GM-CSF, cimetidine, and histamine and are characterized as being positive for surface antigens CD14, CD64, CD80 and CD86, and devoid of surface antigens CD1a, CD1c and CD83, as determined by immunofluorescence staining and flow cytometry analysis. It is noted that the specification discloses no immunofluorescence

staining and flow cytometry analysis data, but merely discloses Applicant's analysis of uncontrolled data as set forth in Tables 1-5. It is the Examiner's position that the cells of the instant claims are much more likely to comprise a mixed cell culture of dendritic cells and macrophages than they are to comprise a single new, and previously undescribed, cell type. This is the Examiner's position particularly in view of the disclosure at page 5 that only 10% of the claimed cells need express CD14, only 10% of the claimed cells need express CD64, only 30% of the claimed cells need express CD80, and only 30% of the claimed cells need express CD86, a description that most certainly describes a mixed cell population.

Applicant's arguments, filed 2/02005, have been fully considered but they are not persuasive. Applicant directs attention to the declaration of Dr. Lotze.

The Declarant indicates that the cells of the instant specification and claims are not a mixed cell population and states that the cells of the claims "have gained acceptance in the scientific community as a new phenotype" known as "Dendritophages®" and directs the Examiner to 2 references.

A review of the literature (as evidenced by a Medline search) yields a single hit searching "Dendritophage®". The reference, Barrou et al. 2004, teaches that a "Dendritophage®" comprises only an autologous dendritic cell (DC). The references cited by the Declarant provide no further description of the cells. The Assignee's (IDM) own website explicitly states that "Dendritophages®" comprise no more than antigen-loaded monocyte-derived DCs (see enclosure). Thus, the Declarant's assertion regarding a new cellular phenotype is not supported by either the art nor the Declarant's employer's own website.

The Declarant states that the specification states that the methods of the instant specification result in new antigen presenting cells; see, for example, Tables 2 and 3. The Declarant admits that the asserted "data" of at least Tables 2 and 3 are essentially meaningless. The Declarant then tries to argue that the "relative" values of the Tables "are highly significant in characterizing the new phenotype".

It remains the Examiner's position that the Tables of the instant specification provide essentially no support for the claimed cell type. The concept of controlled experiments and the comparison of experimental data to known data is well-established. Applicant's could have compared macrophages to DCs

to the MD-APCS of the instant claims in a scientifically controlled fashion. Instead, Applicant's have *chosen* to simply assert that they have arrived at a new cell type, and present said assertions in tabular form. Specifically regarding the Tables of the instant specification, Table 1 discloses uncontrolled yields and simply asserts "a recovery of a large quantity of MD-APCs" after 5-11 days of culture of mononuclear cells". Table 2 discloses asserted phenotypes of the asserted MD-APCs of the instant claims. Note that both the "percentage of positive cells" and the "MIF" (mean intensity fluorescence) are meaningless in the instant uncontrolled context. Regarding Table 3, the "data" is again uncontrolled, but the Declarant states that the results indicate more phagocytosis by the claimed cells than "would be expected" by "a homogeneous population of conventional macrophages". Table 4 comprises no more than "comparative characterization" and Table 5 simply asserts a "complete phenotypic characterization" of unknown source. In total then, these Tables fail to establish in any sort of recognized scientific manner that the cells of the instant claims consist of a new and discrete cell type as asserted by the Declarant.

The Declarant discounts the disclosure of the specification at page 5, lines 18-29 and refers to the disclosure at pages 3, lines 14-21, page 4, lines 1-7, and page 5, lines 1-6 as "data".

It is unclear to the Examiner how any of the disclosures in the Summary of the Invention can in any scientific sense of the word by considered to be "data".

The Declarant asserts that the specification teaches how to make the cells of the instant claims. The Declarant states that histamine and cimetidine were use in combination in the examples most fully described, and in an alternative approach IL-13 was used. The Declarant states that cimetidine blocks TH2 lymphocytes and histamine stimulates unblocked TH2 lymphocytes in the mixed cell culture disclosed at page 11 of the specification.

It is noted that the Declarant's assertions are not reflected in the teachings of the instant disclosure. The specification discloses nothing regarding Th1 and Th2, indeed, the terms are not used in the specification.

The Declarant states that the disclosure does not indicate how IL-13 is to be used, but points to two journal articles as showing that "the new phenotype is produced when IL-13 is used at quite conventional concentrations".

The Declarant grossly mischaracterizes the two cryptically referred to references (references generally include author). Nevertheless, neither of the references, Frison, N., et al., *Biochem. J.* 2002, nor Frison, N., et al. *J. Biol. Chem.* 2003, concern the production of a new cell type. Both reference regard the identification of glycoclusters that bind lectin receptors and both references specifically teach that dendritophages are nothing more than DCs derived from PBMC cultured in GM-CSF and IL-13.

The Declarant states that the cells of the instant claims derive from monocytes cultured in hydrophobic bags.

The Declarant's statement would appear to be an indication that culture in hydrophobic bags comprises an essential step; it is noted that said step was not previously included in the claims and, indeed, now appears only in 2 dependent claims.

Returning to Applicant's arguments, Applicant argues, "the Examiner is respectfully reminded that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed".

Ample evidence that the process of the instant claims would not likely result in the cells of the instant claims has been previously provided. But the skilled artisan need look no farther that the first claim, Claim 44, and note the only actual limitations of the claim are that PBMCs (comprising monocytes and lymphocytes) be cultured with GM-CSF and any other ligand for which a receptor can be found on the surface of said monocyte. Thus, the method of the instant claims would encompass the culture of PBMCs in GM-CSF and glucose. Clearly, the skilled artisan would not expect said culture to result in a novel cell type comprising only the most immunologically useful characteristics of both macrophages and DCs.

Applicant again asserts that previously cited references, Boyer et al. (1999) and Chaperot et al. (2000), support the MD-APCs of the instant claims. Applicant now asserts that the MAC-

DCs of Boyer et al. and the macrophages of Chaperot et al. are the MD-APCs of the instant claims.

As set forth previously, it is again noted, that neither the methods nor the cells of the references are the methods or the cells of the instant specification and claims. Regarding Boyer et al., the reference fails to teach the culture method of the instant specification, but more importantly, the reference fails to teach the cells of the instant claims. As set forth in the specification and reiterated above, the cells of the instant claims are CD1a-, CD80+ and CD86+, the MAK cells of Boyer et al. express CD86 at a lower level and intensity and are essentially devoid of CD80. Additionally, the cells of the instant claims are highly phagocytotic whereas the MAK cells of Boyer et al. are not. It is clear that the cells of Boyer et al. are *not* the cells of the instant claims.

Regarding the methods and cells of Chaperot et al., the macrophages of the reference are produced by the well-known method of culturing monocytes in GM-CSF while the dendritic cells of the reference are produced by the equally well-known method of culturing monocytes in GM-CSF and IL-13. Applicant is simply incorrect in arguing that the macrophages of the reference are cultured with IL-13. The reference clearly states that *the DCs* of the reference result from culture with IL-13.

Applicant argues that the cells of the instant specification result from monocytes cultured in hydrophobic bags.

Applicant is advised that it appears that this limitation should be recited in the independent claims as both Applicant and the Declarant appear to agree that said culture comprises an essential step.

Applicant argues that the specification discloses at least two ways of producing the MD-APCs of the instant claims, culture of monocytes in histamine and cimetidine, or culture in IL-13.

Regarding the culture of monocytes in histamine and cimetidine, this is the most fully disclosed method of the instant specification. But even in this instance, no data is disclosed regarding the functionality of the cells produced, i.e., the ability to stimulate T cells. The only actual mention of T cell stimulation (MLR results) is found in Table 4,

"Comparative characterization of Antigen Presenting Cells"; said cells of unknown source are disclosed as "Stimulation of MLR ++". This sort of vague disclosure is not "data" and is not found to be persuasive in establishing that the methods of the specification and claims result in the production of a novel cell type.

Applicant again misrepresents the teachings of the specification in the assertion that the specification teaches the production of the MD-APCs of the instant claims by culture in IL-13. The specification actually discloses that the cells are produced by culture in IL-13 *and GM-CSF*, and in an uncontrolled experiment the cells are asserted to "strongly increase allogenic lymphocyte stimulation" (page 14).

Interestingly, Applicant's own post-filing publications, Goxe, B., et al. *Res. Immunol.* 1998, and Goxe, B., et al., *Immunol. Invest.* 2000, both clearly teach that the culture of monocytes (or PBMC), with GM-CSF and IL-13, in hydrophobic bags, results in immature DCs, not the MD-APC cell type of the instant claims.

Accordingly, it remains the Examiner's position that the instant specification fails to adequately describe the making of the invention of the instant claims.

6. Claims 44, 49, 50, and newly added Claims 91-104 stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) Monocyte-derived antigen-presenting cells (MD-APCS) having been produced by differentiating blood monocytes in vitro, in the presence of lymphocytes, GM-CSF and at least one ligand having a receptor on the surface of monocytes, said MD-APCS having, when compared with monocyte derived macrophages prepared in the presence of GM-CSF only, higher phagocytic properties of formalin fixed yeast and higher ability for

stimulation of allogenic T lymphocytes, in Claims 44, 97, and 104.

Applicant argues that support for the limitation can be found at page 1-3 of the specification.

Applicant is advised that support for an invention is not likely found in the Background section of a specification; regardless this specific comparison has not been found.

7. The following are new grounds of rejection necessitated by Applicant's amendment.

8. Claims 91-104 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:
All of the limitations of Claims 91-104.

Applicant has not indicated where any support for any of the limitations of the new claims can be found. Applicant has merely stated that support can be found in the original claims and generally throughout the specification.

Upon careful review of the specification no support has been found for the specific combinations of limitations that have been cobbled together in the newly added claims. Some of the limitations, e.g., wherein the MD-APC comprises a surface receptor for the ligand IL-13 (Claim 13) is not found at all (IL-13 is disclosed only in combination with GM-CSF, page 14) are not disclosed at all. Others, e.g., culture in hydrophobic bags (Claims 93 and 101) are broader that the disclosure (only ethylene vinyl acetate and polypropylene hydrophobic bags are disclosed, and then only in specific examples, page 10). Still other claims recite limitations found in one specific example in combination with limitations found in other examples, or in the generic disclosure e.g., the example at page 7 (absent the 5 to 15 days of culture) incorporating the concentrations of reagents

set forth at page 6 (Claim 94). Finally, in Claim 104, the cell of the claim is described by the recitation of selected cell surface markers, CD14, CD64, CD80, and CD86, while other cell surface markers, e.g., HLA-DR are ignored. The specification fails to describe the claimed cells in this selective manner, see for example, Table 2.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 44, 49, 50, and newly added Claims 91-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically:

A) In Claim 44, it is unclear why the word "presence" was deleted; regardless it renders the claim grammatically incorrect.

B) In Claim 93, the claim is again grammatically incorrect in the recitation of a "composition;

removing …;

isolating …;

culturing …" etc. It appears that the word "comprising" after composition is missing.

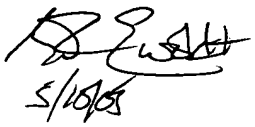
11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.



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